

*Submitted*

*8 juin 2005*

## Declaration

I, Grant A. Kraft, residing in Glenview, IL, USA, declare;

THAT I am presently Chairman and Chief Science Officer of Acumen Pharmaceuticals, Inc., a copy of my C.V. being enclosed herewith;

THAT I have never been an employee of ConjuChem Inc.;

THAT I, as an employee and Chief Technology Officer of Tibotec Inc., collaborated with ConjuChem Inc. on a project related to HIV and specific anti-fusogenic peptides from 1999 to 2001;

THAT, from 1999 to 2001, I was a scientific adviser on the scientific committee of ConjuChem Inc.;

THAT during that mandate, the inventors of the subject-matter described in the European Application No. 00932570.5 discussed with me about the preparation of an anti-fusogenic peptide having a reduced serum clearance and an improved resistance to peptidase degradation by coupling thereto a maleimide group which is reactive with a thiol group on albumin to form a stable covalent bond;

THAT at that time, based on my experience in the field, I was very skeptical about the anti-fusogenic potency of such a construct because of the obstructed access to the targeted sequences on gp41 during or after its folding within the fusion process, and the size of albumin;

THAT I read the European Application No. 00932570.5 of ConjuChem Inc, the Opposition document filed by Trimeris Inc, the response filed by ConjuChem Inc, the Communication accompanying the summons by the European Opposition Division, and the Interlocutory Decision of the Opposition Division;

THAT I found the subject matter of European Application No. 00923570.5 surprising and unexpected in view of the state of the art at the time the invention was made;

THAT I am of the view that the person skilled in the art would have had reasons to doubt that this approach could work because of the difference of mechanisms between the antiviral peptides and the dynorphin peptides. Specifically, the steric demands associated with the interaction between the anti-viral peptides and the viral fusion proteins are high, such that incorporation of a linker group and maleimide would interfere with the necessary anti-fusogenic interactions. This concern would have been sufficiently severe

so as to discourage the person skilled in the art from pursuing this approach. Such considerations are, in my view, beyond routine experimentation;

THAT the person skilled in the art, to the contrary, considering the time and costs involved in this type of experimentation would have considered other approaches since the mechanism of action of antifusiogenic peptides would have been believed to be incompatible with the attachment of the peptide with albumin to provide an extended half-life;

THAT the person skilled in the art would not have expected modification of an antiviral, antifusiogenic peptide with a maleimide group, leading to attachment of the peptide to albumin *in vivo*, to result in a peptide which simultaneously had an extended half-life and also had antifusiogenic activity.



Grant A. Krafft, Ph.D.  
Chairman and Chief Science Officer  
Acumen Pharmaceuticals, Inc.

## CURRICULUM VITAE

Grant Arthur Krafft, Ph. D.

### ADDRESS

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USA

### CONTACT INFORMATION

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### PERSONAL DATA

Married, 2 children; Date of Birth: February 6, 1954

### EDUCATIONAL BACKGROUND

UNIVERSITY OF ILLINOIS - Urbana, Illinois  
Ph.D., Organic Chemistry - 1980  
Research advisor - Professor John A. Katzenellenbogen  
VALPARAISO UNIVERSITY - Valparaiso, Indiana  
B. S. 1976 with Highest Distinction, Special Honors in Chemistry

### PROFESSIONAL EXPERIENCE

#### ACUMEN PHARMACEUTICALS, INC.

South San Francisco, CA  
February, 1996 to present

#### CHAIRMAN AND CHIEF SCIENCE OFFICER

Dr. Krafft is the Chairman and CSO of Acumen, a privately held Alzheimer's drug discovery company. Acumen was founded in 1996 to exploit proprietary technology surrounding amyloid  $\beta$ -derived diffusible ligands (ADDLs), now recognized as the likely cause of Alzheimer's disease. Acumen's ADDL technology was developed by Dr. Krafft and his Acumen co-founders Prof. William Klein at Northwestern University and Prof. Caleb Finch at the University of Southern California. Acumen has established a research and development partnership with Merck and Co. to develop ADDL antibodies and vaccines for treatment of Alzheimer's disease and mild cognitive impairment. Acumen also has established pre-clinical programs focusing on ADDL diagnostics, small molecule ADDL blockers, receptor antagonists and signaling antagonists.

#### TIBOTEC-VIRCO NV AND TIBOTEC, INC.

Rockville, MD, August, 1999 to January, 2000  
**CONSULTANT**

Dr. Krafft was a consultant to Belgium-based Tibotec-Virco NV and Tibotec, Inc., providing expertise in the area of anti-HIV protease inhibitor and anti-fusion drugs.

February, 2000 to January, 2002

#### CHIEF TECHNOLOGY OFFICER

Dr. Krafft served as the Chief Technology Officer for Belgium-based Tibotec-Virco NV and Tibotec, Inc. Tibotec discovered and developed several highly potent anti-HIV drugs with extraordinary activity against highly resistant HIV strains, demonstrating efficacy in early Phase IIa clinical studies. Its Virco subsidiary developed unparalleled expertise in pharmacogenomics and molecular diagnostics directed towards individualized disease management products, services and technologies for HIV, other infectious diseases and cancer. Dr. Krafft reported to the founding CEO of Tibotec-Virco and had worldwide strategic and business development responsibility for Tibotec-Virco's drug discovery technologies. Tibotec-Virco was acquired for \$360M in March, 2002 by Johnson and Johnson.

**EVANSTON NORTHWESTERN HEALTHCARE – ENH RESEARCH INSTITUTE**

Evanston, Illinois

**DIRECTOR, RESEARCH DEVELOPMENT**

June, 1997 to February, 2000

Dr. Krafft served as Director of Research Development for the ENH Research Institute (ENHRI), reporting to the Institute's Chief Administrative Officer. During Dr. Krafft's tenure, Research Institute annual funding grew from \$4M to more than \$15M, and significant new programs were initiated in gene therapy, MRI, cancer genetics and Alzheimer's disease. He was also responsible for development of ENHRI intellectual property portfolio and for technology transfer and licensing activities at ENHRI.

**NORTHWESTERN UNIVERSITY – FEINBERG SCHOOL OF MEDICINE**

**ADJUNCT PROFESSOR, DEPARTMENT OF MOLECULAR PHARMACOLOGY**

Chicago, Illinois, 2004-present

Dr. Krafft is currently Adjunct Professor in the Department of Molecular Pharmacology and Biological Chemistry.

**RESEARCH PROFESSOR, DEPARTMENT OF MOLECULAR PHARMACOLOGY**

1995 to 2003

Dr. Krafft held the academic appointment of Research Professor of Molecular Pharmacology and Biological Chemistry at Northwestern University's Feinberg Medical School. He was a fellow of the Buehler Center on Aging, a member of the Integrated Biological Sciences Program, and a member of the Northwestern University Institute for Neuroscience. Dr. Krafft was Principal Investigator on two NIA-funded Program Projects, in addition to other NIH and Alzheimer's Association grants.

**ABBOOTT LABORATORIES**

Abbott Park, Illinois

**NEUROSCIENCE RESEARCH, PHARMACEUTICAL PRODUCTS DIVISION**

**SENIOR GROUP LEADER, PROGRAM DIRECTOR, ALZHEIMER'S DRUG DISCOVERY**

March, 1994 to February, 1995

Dr. Krafft served as Senior Group Leader and Program Director for Alzheimer's Drug Discovery within Abbott's Pharmaceutical Products Division. This program ran one of the earliest focused searches for the amyloid secretases and conducted detailed structural and biophysical studies of fibrillar amyloid aggregates. Dr. Krafft's group published the first atomic force microscopy studies of amyloid fibrils, documenting the concept that multiple amyloid structures could be involved as the cause of AD.

**DRUG DESIGN AND DELIVERY, PHARMACEUTICAL PRODUCTS DIVISION**

**ASSOCIATE RESEARCH FELLOW, SENIOR GROUP LEADER,**

November, 1991 to February, 1994

Dr. Krafft was an Associate Research Fellow and Senior Group Leader, heading Abbott's Molecular Diversity and Bio-Organic Chemistry Department within Pharmaceutical Discovery and reporting to Dr. Thomas Perun, Divisional Vice-President, Pharmaceutical Discovery. During this period, Dr. Krafft established Abbott's multidisciplinary Alzheimer's Drug Discovery Program, which was funded by the National Institute on Aging as one of six Drug Discovery Groups for Alzheimer's disease. Dr. Krafft also initiated and built Abbott's combinatorial chemistry effort, interfacing library synthesis with related screening strategies in new lead identification within the Pharmaceutical Products Division.

**ABBOTT DIAGNOSTICS DIVISION, R & D LAB HEAD, MOLECULAR PROBE DESIGN**  
June, 1988 to October, 1991

Dr. Krafft was recruited to Abbott's Diagnostics Division to create an exploratory bio-organic chemistry research group. This group developed organic probe molecules to study enzyme and receptor targets (e.g. HIV and HTLV-1 proteases, renin, urokinase, cyclophilin, FKBP) and to identify new diagnostic markers and drug targets. Major contributions included development of the first continuous assay format for HIV protease and renin and their inhibitors, leading to the discovery of Abbott's successful AIDS drug ritonavir, and its follow-on drug, Lopinavir. Dr. Krafft also invented a new homogeneous immunoassay technology, Catalyst Modulation Immunoassay (CAMIA), based on designed, site-directed mutant signaling enzymes.

**SYRACUSE UNIVERSITY**

Syracuse, New York  
1982 to 1988

**ASSISTANT PROFESSOR OF CHEMISTRY**

Dr. Krafft's research focused on new synthetic methodology and on the design of organic probe molecules for biological and biophysical studies. His group developed the first synthesis of "caged" fluorescein and other classes of photoactivatable fluorophores, pioneering the development of a new biophysical technique to study molecular diffusion and transport, fluorescence photoactivation and dissipation (FPD). Dr. Krafft's group discovered the first techniques to prepare highly reactive selenoaldehydes and selenoketenes, providing initial insights into reactivity in cycloaddition reactions. His research was supported by major grants from NIH, NSF and the American Cancer Society, and by other foundation awards.

**UNIVERSITY OF WISCONSIN**

Madison, Wisconsin  
1980-1982

**NIH POST-DOCORAL FELLOW**

Dr. Krafft was an NIH post-doctoral fellow, conducting research with Prof. Edwin Vedejs in the Chemistry Department at UW-Madison. His synthetic studies were directed towards cytochalasin D and phorbol esters.

**OTHER PROFESSIONAL ACTIVITIES**

Dr. Krafft serves on the Board of Trustees of Valparaiso University, Valparaiso, IN.

Dr. Krafft has consulted for pharmaceutical and biotechnology companies, and for venture capital funds. Dr. Krafft also serves on or has served on NIH, NSF, and Alzheimer's Association review panels and the DOD Breast Cancer Initiative.

**HONORS AND AWARDS**

T. L. L. Temple Awardee, Alzheimer's Association, 1998-1999

Distinguished Alumni Achievement Award, Valparaiso University, 1993

Abbott Laboratories Volwiler Society Research Fellow, 1992

Abbott Diagnostics Division, Technical Advisory Board Research Award, 1990

American Cancer Society Junior Faculty Research Award, 1983-1986

National Institutes of Health Postdoctoral Fellow, 1980-1982

University of Illinois, Proctor and Gamble Graduate Fellow, 1976-1978

American Chemical Society Undergraduate Analytical Chemistry Award, 1976

Special Honors in Chemistry, Valparaiso University, 1976

### SOCIETIES

American Chemical Society  
American Association for the Advancement of Sciences  
Society for Neuroscience

### EXTRAMURAL RESEARCH SUPPORT

National Institutes of Health, National Institute for Aging  
"Supramolecular A $\beta$  Structure and Glial-Neuronal Responses"  
Grant A. Kraft - Principal Investigator  
\$3.1 MM total costs, June 1, 1997 - May 31, 2002

National Institutes of Health, National Institute for Aging  
"Structure and Function of Alzheimer's A $\beta$  Aggregates"  
Grant A. Kraft - Principal Investigator  
\$1.3 MM total costs, September 1, 1996 - August 31, 2001

Alzheimer's Association  
"Discovery of Fyn SH2 Ligands as Potential Alzheimer's Therapeutics"  
Grant A. Kraft - Principal Investigator  
\$250 K total costs, January 1, 1998 - December 31, 2000

National Institutes of Health, National Institute for Aging  
Drug Discovery Group-Alzheimer's Disease  
"Neural Proteases: New Alzheimer's Disease Drug Targets"  
Grant A. Kraft - Principal Investigator  
\$3.9 MM total costs, October 1, 1991 - July 31, 1996

National Science Foundation  
"Selenoaldehydes: New Versatile Synthetic Intermediates"  
Grant A. Kraft - Principal Investigator  
\$147,000 total costs - March 1, 1987 - Feb. 28, 1990.

National Institutes of Health Grant #1RO1 GM33864  
"Photoactivatable Fluorophores: Site Selective Biological Probes"  
Grant A. Kraft - Principal Investigator  
\$233,520 direct costs - July 1, 1984 - June 30, 1987.

National Institutes of Health Grant #1R23 CA35954  
"Simplified Cytochalasins as Specific Probes of Cytoskeletal Function"  
Grant A. Kraft - Principal Investigator  
\$105,000 direct costs - August 1, 1983 - July 31, 1986.

American Cancer Society  
Junior Faculty Research Award  
Grant A. Kraft - Principal Investigator  
\$63,000 direct costs - July 1, 1983 - June 30, 1986.

Petroleum Research Fund, American Chemical Society, G Award, #14623  
"Cleavable Thianes in Acyclic Stereocontrol and Macrocycle Formation"  
Grant A. Kraft - Principal Investigator  
\$15,000 direct costs - September 1, 1983 - August 31, 1986.

Research Corporation Grant #9868, Grant A. Kraft - Principal Investigator  
"Stereospecific Removal of Sulfur via Transition Metal Insertion Reactions"  
Grant A. Kraft - Principal Investigator  
\$14,000 direct costs - January 1, 1983 - December 31, 1984.

## PUBLICATIONS

1. Krafft, G. A.; Katzenellenbogen, J. A. "Synthesis of Haloenol Lactones. Mechanism-Based Inactivators of Serine Proteases" *J. Am. Chem. Soc.* 1981, 103, 5459-5466.
2. Chakravarty, P. K.; Krafft, G. A.; Katzenellenbogen, J. A. "Haloenol Lactones: Enzyme-activated Irreversible Inactivators for Serine Proteases" *J. Biol. Chem.* 1982, 257, 610-612.
3. Krafft, G. A.; Reich, M. F.; Katzenellenbogen, J. A. "Synthesis of <sup>14</sup>C-Labeled 10,11-Epoxyfarnesyl Diazoacetate. A Potential Photoaffinity Labeling Reagent for Insect Juvenile Hormone Binding Proteins" *J. Labeled Cmpds Radiopharm.* 1982, 19, 591-4.
4. Vedejs, E.; Krafft, G. A. "Cyclic Sulfides in Organic Synthesis" *Tetrahedron* 1982, 38, 2857-2881.
5. Vedejs, E.; Krafft, G. A.; Arnott, M.; Eustache, J. "A Model for Cytochalasin D: Synthesis of a Cycloundecenone by Sulfur Ylide Ring Expansion" *J. Org. Chem.* 1982, 47, 4384-4386.
6. Krafft, G. A.; Meinke, P. T. "Functionalization of Furans via Phenacyl Sulfides" *Tetrahedron Letters* 1985, 26, 135-140.
7. Krafft, G. A.; Meinke, P. T. "Generation of Thioaldehydes via  $\alpha$ -Silyl Disulfides", *Tetrahedron Letters* 1985, 26, 1947-1950.
8. Krafft, G. A.; Siddall, T. L. "Stereospecific Displacement of Sulfur from Chiral Centers. Activation via Thiaphosphonium Salts." *Tetrahedron Letters* 1985, 26, 4867-4871.
9. Krafft, G. A.; Cummings, R. T.; Dizio, J. P.; Furukawa, R.; Brvenik, L. J.; Sutton, W. R. and Ware, B. R. "Fluorescence Photoactivation and Dissipation (FPD)." pp. 35-52 in Nucleocytoplasmic Transport, (R. Peters, M. Trendelburg, eds.) Springer Verlag, Berlin, 1986.
10. Ware, B. R.; Brvenik, L. J.; Cummings, R. T.; Furukawa, R.; and Krafft, G. A. "Fluorescence Photoactivation and Dissipation." pp. 141-157 in Applications of Fluorescence in the Biomedical Sciences (D. L. Taylor, F. Lanni, R. Murphy, and A. Waggoner, eds.) Alan R. Liss, Inc., New York, 1986.
11. Krafft, G. A.; Meinke, P. T., "Selenoaldehydes: Preparation and Dienophilic Reactivity." *J. Am. Chem. Soc.* 1986, 108, 1314-1317.
12. Krafft, G. A.; Garcia, E. A.; Guram, A.; O'Shaughnessy, B.; Xu, X. "Simplified Cytochalasins. 1. Synthesis of Versatile Perhydroisoindolone Intermediates." *Tetrahedron Lett* 1986, 27, 2691-2694.
13. Meinke, P. T.; Krafft, G. A. "Selenofluorenone: Synthesis and Cycloaddition Chemistry" *Tetrahedron Letters*, 1987, 28, 3887-3890.
14. Meinke, P. T.; Krafft, G. A. "Regiochemical Preferences in Selenoaldehyde Cycloadditions" *Tetrahedron Letters*, 1987, 28, 3887-3890.
15. Cummings, R. T.; Krafft, G. A. "Photoactivatable Fluorophores. 1. Synthesis and Photo-activation of o-Nitrobenzyl-Quenched Fluorescent Carbamates" *Tetrahedron Lett* 1988, 29, 65-68.
16. Cummings, R.; DiZio, J.; Krafft, G. A. "Photoactivatable Fluorophores. 2. Synthesis and Photo-activation of Functionalized 3-Aroyl-2-FurylChromones" *Tetrahedron Lett* 1988, 29, 69-72.
17. Krafft, G. A.; Sutton, W.; Cummings, R. "Photoactivatable Fluorophores. 3. Synthesis and Photo-activation of Fluorogenic Difunctionalized Fluorescins" *J Am Chem Soc* 1988, 110, 301-302.
18. Meinke, P. T.; Krafft, G. A. "The Synthesis and Cycloaddition Reactivity of Selenoaldehydes." *J. Amer. Chem. Soc.* 1988, 110, 8671-8679.
19. Meinke, P. T.; Krafft, G. A. "Preparation and Cycloaddition Reactions of Selenoketones." *J. Amer. Chem. Soc.* 1988, 110, 8679-8675.
20. Meinke, P. T.; Krafft, G. A.; Guram, A. "Synthesis of Selenocyanates via Cyanoselenation of Organocuprates" *J. Org. Chem.* 1988, 53, 3632-3634.
21. Walling, E.; Krafft, G. A.; Ware, B. R. "Actin Assembly Activity of Cytochalasins and Cytochalasin Analogs Assayed Using Fluorescence Photobleaching Recovery." *Arch. Biochem. Biophys.* 1989, 264, 321-32.
22. Wang, G. T.; Matayoshi, E. D.; Huffaker, H. J.; Krafft, G. A. "Design and Synthesis of New Fluorogenic HIV Protease Substrates Based on Resonance Energy Transfer" *Tetrahedron Letters* 1990, 31, 6493-6496.

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29. Ziernicka-Merchant, B., Aran, J. M., Plagemann, P. G. W., Krafft, G. A. "Effects of Chemical Modification of NBTI on its Binding to High Affinity Binding Sites and Inhibition of Nucleoside Transport" *Biochem. Pharm.* 1992, 41, 1577-1583.
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33. Krafft, G. A. "Amyloid and Alzheimer's Disease: A Critical Review" *Ann. Rep. Med. Chem.* 1993, 28, 49-58.
34. Krafft, G. A., Wang, G. T. "Fluorescent Probes in Studies of Proteases" in Fluorescent Chemosensors for Ion and Molecular Recognition, A. Czarnik, ed. ACS Symposium Series, Vol. 538, pp 183-195, Washington, DC, 1993.
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36. Wang, G. T., Lane, B., Fesik, S. W., Petros, A., Luly, J., Krafft, G. A. "Synthesis and FKBP Binding of Small Molecule Mimics of the Tricarbonyl Region of FK506" *BioMed Chem Lett.* 1994, 4, 1161-1166.
37. Krafft, G. A., Wang, G. T. "Synthetic Approaches to Continuous Assays of Retroviral Proteases" *Methods in Enzymology*, 1994, 241, 70-86.
38. Ladror, U. S., Snyder, S. W., Wang, G. T., Holzman, T. F., Krafft, G. A. "Cleavage at the Amino and Carboxy Termini of Alzheimer's Amyloid- $\beta$  by Cathepsin D" *J. Biol. Chem.* 1994, 269, 18422-8.
39. Pope, W., Lambert, M. P., Leypold, B., Seupaul, R., Sletten, L., Krafft, G., Klein, W. L. "Microtubule-associated Protein Tau is Hyperphosphorylated during Mitosis in the Human Neuroblastoma Cell Line SH-SY5Y" *Exptl. Neurof.* 1994, 126, 185-94.
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41. Snyder, S. W., Ladror, U. S., Wade, W. S., Wang, G. T., Barrett, L., Matayoshi, E. D., Krafft, G. A., Holzman, T. F. "Amyloid- $\beta$  Aggregation: Inhibition of Aggregation in Mixtures of Amyloid with Different Chain Lengths" *Biophys. J.* 1994, 67, 1216-28.
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